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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,691	10/14/2004	David Hands	20974YP	9304
210 7590 01/31/2008 MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907			EXAMINER ANDERSON, REBECCA L	
			ART UNIT 1626	PAPER NUMBER
			MAIL DATE 01/31/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 10/511,691	<b>Applicant(s)</b> HANDS ET AL.	
	<b>Examiner</b> Rebecca L. Anderson	<b>Art Unit</b> 1626	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 15 January 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

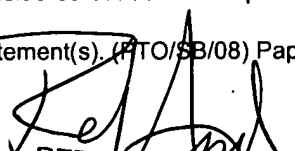
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: \_\_\_\_\_.
- Claim(s) objected to: \_\_\_\_\_.
- Claim(s) rejected: 15, 16 and 18-27.
- Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

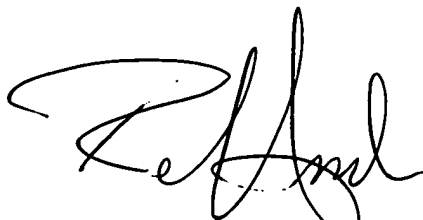
11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_
13. ☐ Other: \_\_\_\_\_.

  
 REBECCA ANDERSON  
 PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: For essentially the same reasons as found in the final rejection mailed 15 January 2008, the 35 USC 103(a) rejection is maintained as:

- 1) the temperature of the cyclization process; The prior art reference provides in example 75 that 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methylcarboxyacetamidrazono)morpholine (which corresponds to applicants formula 4) in 15ml of xylenes was heated at reflux for 2 hours. Heated at reflux in xylenes corresponds to applicants temperature of 140-150 degrees Celsius as can be seen in the CRC Handbook of Chemistry and Physics wherein the boiling points of the xylene solvents are 138, 139 and 144 degrees Celsius;
- 2) the use of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine; The prior art reference provides motivation to use the hydrochloride salt as the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurrying in a mixture of toluene and sodium bicarbonate.
- 3) the use of toluene; The prior art reference provides motivation to toluene as the prior art reference as the prior art reference provides in another process of preparing substituted heterocycles of the structure as found on column 5, the use of an HCl salt and toluene, see example 101, column 131 wherein the hydrochloride salt of the product was broken by slurrying in a mixture of toluene and sodium bicarbonate.
- 4) the use of an inorganic base (such as potassium carbonate); The prior art reference provides motivation to use an inorganic base as diisopropylethylamine is used in example 75 as the base, additionally, the prior art reference provides the use of appropriate bases to include diisopropylethylamine, potassium carbonate, sodium carbonate and the like on column 65 and utilizes the inorganic base of potassium carbonate in example 83, column 107 with the polar aprotic solvent of DMF.
- 5) the use of a polar aprotic solvent (such as dimethylsulfoxide or dimethylformamide); The prior art reference provides motivation to use a polar aprotic solvent as acetonitrile is used in example 75 as a polar aprotic solvent, additionally, the prior art reference provides the use of other polar aprotic solvents in the preparation of the substituted heterocycles of the structure as found on column 5, see example 83 wherein DMF is used; or
- 6) the use of an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization. The prior art reference provides motivation to use an aqueous wash as the prior art provides washing with sodium bicarbonate in example 101, column 131. Additionally, applicants' argue that even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147 as the present invention gives the desired compound in 85% yield (page 8, lines 8-9) which is unexpectedly higher than the yield disclosed for the procedure in the '147 patent (79% yield, example 75, column 104). This argument is not persuasive as applicant has not provided a showing as stated in MPEP 716.02(a) and (b) that the results were greater than those which would have been expected from the prior art to an unobvious extent and that the results are of a significant, practical advantage. Specifically, any difference between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. The example in the specification (page 8, lines 8-9) and example 75 of the prior art reference does not discuss how or provide a showing that the differences in results are in fact unexpected an unobvious and of both statistical and practical significance. Applicant has the burden of explaining the data they provide as evidence of non-obviousness. Additionally, applicant has failed to provide a showing of sufficient scope as the example 1(pages 7 and 9) requires specific reaction conditions, such as, for example, the use of potassium carbonate, not just any inorganic base as claimed.

Applicant has failed to provide a showing of sufficient scope, and failed to further show that the results are greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.



REBECCA ANDERSON  
PRIMARY EXAMINER